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ART UNIT	**PAPER NUMBER**
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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trad marks

Office Action Summary	Application No. 09/341,894	Applicant(s) Piechaczyk et al.
	Examiner Peter Brunovskis	Group Art Unit 1632

☐ Responsive to communication(s) filed on _____.

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-20* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-20* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☒ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☒ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☒ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). 6

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Information Disclosure Statement

FR 2,706,486 was only considered with respect to the English abstract, since no translation was supplied.

Specification

35 U.S.C. 112, first paragraph, requires the specification to be written in "full, clear, concise, and exact terms." The specification is replete with terms which are not clear, concise and exact. The specification should be revised carefully in order to comply with 35 U.S.C. 112, first paragraph. Examples of some unclear, inexact or verbose terms used in the specification include the same errors recited in the 35 U.S.C. 112 2nd paragraph rejections below..

The abstract of the disclosure is objected to because it inappropriately employs legal phraseology, including "said" (lines 7, 8, 10, 11). Correction is required. See MPEP § 608.01(b).

Claim Objections

Claims 1-5, 12-16, and 20 (and dependent claims) are objected to because of the following informalities:

The form of the claims is objected since each claim must be the object of a sentence starting with "I (or we) claim", "The invention claimed is" (or equivalent). See MPEP § 608.01(m).

In claim 1, the "," of line 10 should either be deleted or an additional --,-- should be added between "antibody" and "or".

Claims 3 and 4 are objected to because they fail to comprise a single sentence. See MPEP § 608.01(m).

In claim 5, line 2, "biological" should be deleted since viral vectors are inherently "biological".

In claim 12, "chimerical", defined in the Encyclopedia Britannica Online dictionary as "existing only as the product of unchecked imagination or "given to fantastic schemes", should be changed to --chimeric--, defined in the Online dictionary as "relating to, derived from, or being a genetic chimera or its genetic material".

In claim 13, line 4, and claim 14, lines 4 and 5, "specific" should be deleted since the "antibody, fragment, or antibody derivative" (in cl. 13) or the "antibody fragment or antibody derivative" (in cl. 14) would be inherently directly against either the "specific tumor cell antigen" or the "specific antigen".

Independent claims 15 and 20 should begin with --A--. Also, in claim 15, line 1, "comprised of a" should be changed to --comprising a--. In claim 16, line 1, "human or non-human" should be deleted since "human or non-human" doesn't exclude any type of cell, nor is it given any patentable weight.

Appropriate correction is required.

Claim 2 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim, or amend the claim to place the claim in proper dependent form, or rewrite the claim in independent form.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-20 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims are generally narrative and indefinite, failing to conform with current U.S. practice. They appear to be a literal translation into English from a foreign document and are replete with grammatical and idiomatic errors.

Claim 1 is improperly directed to two distinct inventions, nucleic acids and cells comprising the nucleic acids, wherein each of these inventions bears a separate classification. Each claim should be directed to a single invention.

Claim 1 (and dependent claims) recites the limitation "its previous culture" in line 6. There is insufficient antecedent basis for this limitation in the claim. Also "the secretion" (line 9), "the blood circulation" (line 9), and "this antibody or a fragment of it" (line 10) lacks antecedent basis.

In claim 1, "[b]iological material" is indefinite since it is unclear *which part* of the biological material is used for preparing the pharmaceutical compositions. Claim 1 is further rendered indefinite by the phrase, "in a form enabling *in vivo* transfer" in line 3 and "in a form enabling its incorporation into the mammal's organism" in lines 5 and 6 since it is not clear what limitations or metes and bounds comprise "enabling" and "incorporating" in the two contexts and since use of the possessive form in "mammal's organism" suggests in situ incorporation into a fetus or even incorporation into a resident "micro"organism. Moreover, it is unclear how "previous culture" (line 6) relates to "enabling its incorporation". The phrase "the mammal not naturally producing antibodies" (line 4) further renders claim 1 indefinite since it is not clear if "antibodies" refers to a mammal that doesn't naturally produce antibodies, such as a SCID mouse, or to a mammalian cell type that doesn't "naturally produce antibodies". Also, it is not clear *which mammal* is being referred to (the mammal for which the biological material is prepared for or a cell from *any mammal*). Additionally, it is unclear what "a previous nucleic acid sequence" (line 5) refers to--the nucleic acid sequence of line 2 or some other sequence. It is further noted that "said nucleic acid" in 7 is indefinite since it is unclear whether the nucleic acid of line 7 refers to the nucleic acid of line 2 or line 5. Also it is not clear what "by cells" in line 10 refers to--elements for expressing ? antibodies? Moreover it is not clear what "genetically modified" refers

to in lines 4 and 10. In line 4 it is unclear whether "genetically modified" refers to the "cell of the mammal" or the "antibodies"; in line 10 it is unclear whether it refers to the mammal itself (e.g. transgenic or chimeric) or a mammal comprising genetically modified cells or antibodies. The first two lines at the top of the amendment of 12/15/99, page 2, are incomprehensible in their present context since they comprise a partial sentence that follows the completed sentence of amended claim 1 which ends in a period.

Claims 1-4 and 20 (and dependent claims) are rendered indefinite by their recitation of "not naturally producing antibodies" since it is not clear whether this phrase refers to "cell" or "mammal".

Claims 1-4, 6, 12, 16, and 20 (and dependent claims) are rendered indefinite by their recitation of a "gene", since there is no clear consensus definition in the art accurately delimiting the metes and bounds of "a gene"particularly in view of alternative splicing and uncertainties surrounding the metes and bounds of cis-acting sequences regulating mRNA expression.

Claims 1, 2, 6, and 16 (and dependent claims) are rendered indefinite by their poor wording wherein the claims recite "and elements for expressing *in vivo* said antibody gene and the secretion in the blood circulation *of a* mammal *of a* therapeutically effective amount of this antibody..." (cl. 1, 2, 6) or "and elements guaranteeing the expressing *in vivo* of said antibody gene and the secretion in the blood circulation *of a* mammal *of a* therapeutically effective amount of this antibody..." First, these claims need to be better worded and/or punctuated. The second "of" (i.e. in of a therapeutically effective..) should be deleted. Also, the recitations inappropriately

suggest that *a mammal* is secreted into "the blood circulation". Additionally, it is not clear how the recited "elements" relate to "secretion" or what structural limitations or circumstances are applied to "elements" in claim 16 to "guarantee" the expression *in vivo* of..."

In claims 2-14, and 20 (and dependent claims) the term "[b]iological material" (e.g. cl. 3), the phrase "[b]iological material...according to" (e.g. cl. 10) or "...in accordance to" (e.g. cl. 13), and the phrase "[m]anufacturing process for a cell according to..." (i.e. cl. 20) are indefinite since it is unclear what "biological material" or "cell" is being referred to in the context of these claims. There are multiple "biological material" and "cell" embodiments recited in claim 1 (and in its dependent claims). Consequently, the meaning of "it" (line 1) is also indefinite in claims 3, 4, and 6.

Claim 3 is rendered indefinite by the phrase "[t]his sequence is a complex" since the meaning of "complex" is unclear the present context--does it refer to the sequence itself or does the "complex" comprise additional embodiments apart from "[the] sequence"? Additionally, the meaning of "conjugated" is unclear in the context of "[the] sequence" since "sequences" cannot be conjugated (whereas *nucleic acids* can be "conjugated"). It is further noted that "molecule" in line 6 is vague and indefinite since "molecule" reads on H_2O etc.

Claim 4 (and dependent claim 5) is rendered indefinite by the phrase "[t]his sequence is a vector" since a "sequence" cannot be a vector (a plasmid can be a vector though). Also the meaning of "permitting" (line 6) is indefinite since it is unclear how the sequence (or even the vector) "permit" effective transfer. "Permit" simply means "not prevent" and would therefore

carry little, if any, patentable weight. Also recitation of "effective transfer" is indefinite. Since the vector presumably carries the "antibody gene" it inherently provides "effective transfer". Moreover, it is not clear whether "transfer" refers to systemic circulation, transfer into a cell, or transfer resulting in expression of the antibody transgene.

Claim 6 (and dependent claims) is rendered indefinite by the term "form" in line 2 since the nature of term is unclear as is its is relation to "permit[ting] their incorporation into the mammal's organism". "[P]ermits" simply means "not prevent" and would likely carry little patentable weight in its present recitation. Also, the meaning of "incorporation" and "mammal's organism" are both unclear in the present context since the nature of the incorporation is unclear and since use of the possessive form in "mammal's organism" suggests in situ "incorporation" into a fetus or even incorporation into a resident "micro"organism. Further, it is unclear what "their" in line 2 refers to--biological material, cells, or antibodies, nor is it clear what or "its" (line 3) refers to. Furthermore "its previous culture" lacks antecedent basis and its meaning is indefinite in the context of "incorporation". Moreover, it is unclear *which* cells comprise the "[s]aid cells" of line 4, the cells in line 4 of claim 1 or the cells recited in lines 4 and 5 of claim 1 which are genetically modified *in vitro*. Also, in line 6 "this antibody or a fragment of it" lacks antecedent basis.

Claims 7 and 8 are rendered indefinite by their recitation of "cells" and "mammal" in line 3 of claim 7 and in lines 3 and 4 of claim 8 since it unclear which cells are being referred to--those from *any mammal*, any mammal of the same animal type or species, the same mammal as the one to be treated, or the "mammal's organism" of claim 6.

Claims 7 and 8 are rendered indefinite by their recitation in line 3 of "the cells" and "come from" since it is unclear which "cells" are being referred to, how "come from" is defined, or what the structural relationship is between the "cells" and the "mammal".

Claim 8 is rendered indefinite by its recitation, "and have undergone treatment" since it is unclear what has undergone treatment--the biological material, the cells, the antibodies, or the mammal to be treated by gene transfer. Consequently, the meaning of "them" in line 4 is indefinite as is the meaning of "compatible" in line 5 (compatible in what way?). Morover, it unlcear what "treatment" embraces; e.g. treatment for what? by what?

Claim 9 (and dependent claims) is rendered indefinite by its recitation of the phrase "ability to be able to secrete" since applying the limitations of this phrase requires a further knowledge of the structural relationship between the "biological material" and the "mammal" recited in line 4. Presently the phrase carries little, if any, patentable weight since *any cell* is inherently *capable* of secreting proteins into the blood circulation of a mammal, especially when administered by intravenous injection. Claim 9 is also rendered indefinite by its recitation of "long life" since this is inherently vague and indefinite, but even more so when considering different mammals which have different lifespans or comprising uncertain lifespans (i.e. mammal's organism or fetus).

Claim 10 (and dependent claims) is rendered indefinite by its recitation of "those which may be easily be sampled" since it is unclear what "those" refers to-- "cells not naturally producing antibodies" which are easy to sample or those cells, chosen to "produc[e]" antibodies, and that are easy to sample; further, the metes and bounds of "easily...sampled" are unclear and it

is unclear whether "easily" also applies to "genetically modified ex vivo" and/or "implant[ation] in a mammal".

Claim 12 (and dependent claims) is rendered indefinite by its recitation of "virgin antibody" in line 2 as applied to its definition recited on p. 5, lines 7, 8, since a "natural antibody" is not encoded by "a gene" but rather comprises the product of *two* genes encoding a light chain and a heavy chain. Also, "derivative" is indefinite since the definition or derivative in this context, including its metes and bounds, are not disclosed.

In claim 13, line 3, "[said] antibody derivative" lacks antecedent basis.

In claim 14 "said antibody fragment" (line 3), "[said] antibody derivative" (lines 3, 4), "the virus" (line 4), and "cells" (line 5) lack antecedent bases.

Regarding claim 15, the phrase "preferably" renders the claim indefinite because it is unclear whether the limitations following the phrase are part of the claimed invention. See MPEP § 2173.05(d). The claim is also rendered indefinite by its recitation of "associated with" in line 2 since neither the structural limitations, nor its metes and bounds have been disclosed.

In claim 16 (and dependent claims) "having received said cells" (lines 4, 5) and "this antibody or a fragment of it" (lines 5, 6) lack antecedent bases.

Claim 20 is extremely poorly worded and makes little sense. The phrase "by cells of said mammal genetically modified by said nucleic acid sequence and not producing antibodies naturally in cells not naturally producing antibodies" makes no sense and it is unclear what this phrase relates to--the manufacturing process, the mammal etc. Additionally, it is impossible to

determine among the "cells" recited in lines 1, 5, 7, 8, and 9, how the different "cells" relate to one another or to the other structural limitations of the claim. Moreover, claim 20 recites a process for a cell that is drawn to *any cell* (see cl. 16); however, claim 20 recites limitations that only apply to mammals. Claim 20 is further rendered indefinite by its recitation, "using any appropriate method" since it is unclear what methods are being referred to or what structural or functional limitations apply to a method that is "appropriate". Also, it is not clear how the recited "elements" in line 3 relate to "secretion" in 4 or what structural limitations or circumstances are applied to the "elements" that they "guarantee the expression *in vivo* of...".

Claims 17-19 provide for the use of biological material or nucleic acid sequences, but, since the claims do not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

Claims 17-19 are rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd.* v. *Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any

> person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-20 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Although claims 17-19 recite non-statutory embodiments not subject to examination, to the extent that the claims are amended to recite pharmaceutical vector compositions or their use in methods for in vivo administration to patients in need thereof, the claims read on gene therapy which are not enabled by the present disclosure.

The factors to be considered in determining enablement are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation....Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations" (Wands, 8 USPQ2d 1404). Factors that can be used in evaluating undue experimentation include: the quantity of experimentation necessary, the amount or direction or guidance presented, the presence or absence of working

examples, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, and the breadth of the claims.

Nature of the invention and state of the prior art. Although the claims of the instant invention are broadly drawn to embodiments containing functional use limitations that carry no patentable weight, to the extent that they recite pharmaceutical formulations for ex vivo or in vivo gene therapy they are not enabled by the instant disclosure. At the time the instant application was filed, successful use of gene therapy was not routinely obtainable by those skilled in the art. W. French Anderson, one skilled in the art, recently concluded: "[e]xcept for anecdotal reports of individual patients being helped, there is still no conclusive evidence that a gene-therapy protocol has been successful in the treatment of a human diseases [Nature, vol. 392:(Supp.), 1998, p. 25, first paragraph]...[s]everal major deficiencies still exist including poor delivery systems, both viral and non-viral, and poor gene expression after genes are delivered. The reason for the low efficiency of gene transfer and expression in human patients is that we still lack a basic understanding of how vectors should be constructed, what regulatory sequences are appropriate for which cell types, how *in vivo* immune defenses can be overcome, and how to manufacture efficiently the vectors that we do make" (p. 30, next to last paragraph). Concurring with Anderson, Verma and Somia state that "[t]he Achilles heel of gene therapy is gene delivery...and [t]hus far, the problem has been an inability to deliver genes efficiently and to obtain sustained expression" (Nature, vol. 389, 1997, p. 239, col. 3, 2nd paragraph)...[a]lthough more than 200

clinical trials are currently underway worldwide, with hundreds of patients enrolled, there is still no single outcome that we can point to as a success story" (p. 239, col. 1, 2nd paragraph).

Although the instant disclosure recites ex vivo gene therapy experiments comprising myoblast transplantation in mice, it should be noted that at the time the instant application was filed, successful ex vivo gene therapy comprising myoblast transplantation had not yet been achieved as evidence by clinical trials involving patients with muscular dystrophy (Skuk et al., Exp. Neurol., 155:22-30, 1999; see 2nd paragraph of Introduction on p. 22). In the case of myoblast transfer, Jeffery Leiden, a skilled artisan, illustrated the "difficulties involved in translating gene therapy from the bench to the bedside (N. Engl. J. Med., 333:871-873). Leiden summarized the recent work by others: "Mendell and coworkers evaluated the efficacy of myoblast transfer for the treatment of Duchenne's muscular dystrophy. Previous studies in animals had demonstrated that cultured myoblasts are efficiently incorporated into mouse myotubes after intramuscular injection. However, the present study showed little or no persistence of injected myoblasts in 11 or 12 boys treated and there was no improvement in the strength of the muscle that received injection in any of the patients over the six months of the trial" (p. 871, right column). Leiden goes on to say (p. 872, first full paragraph) that "human muscle appears to be a much less fertile bed for myoblast fusion than its murine counterpart. In addition, immune responses directed against the injected myoblasts may have prevented the stable engraftment of myoblasts".

The specification does not address the problems discussed above and it does not provide an adequate written description teaching one of ordinary skill in the art how to make and use the claimed invention for delivery of polynucleotides encoding secretable antibodies by *in vivo* gene therapy or for *ex vivo* delivery of cells genetically modified to secrete antibodies.

Breadth of claims. The claims are extremely broad, encompassing a potentially limitless range of embodiments.

Predictability of the art. The physiological art is recognized as unpredictable (MPEP 2164.03). As set forth in *In re Fisher,* 166 USPQ 18 (CCPA 1970), compliance with 35 USC 112, first paragraph requires:

> that scope of claims must bear a reasonable correlation to scope of enablement provided by specification to persons of ordinary skill in the art; in cases involving predictable factors, such as mechanical or electrical elements, a single embodiment provides broad enablement in the sense that, once imagined, other embodiments can be made without difficulty and their performance characteristics predicted by resort to known scientific laws; in cases involving unpredictable factors, such as most chemical reactions and physiological activity, scope of enablement varies inversely with degree of unpredictability of factors involved.

In view of Anderson et al. and Verma et al. above, gene therapy is inherently unpredictable since it involves introduction of artificially created compositions into a highly complex milieu presenting a multitude of counteracting forces which have collectively served to undermine most, if not all, attempts to achieve clinical efficacy though gene therapy.

Guidance and working examples. The instant disclosure provides little guidance teaching one of ordinary skill in the art how to make and use the claimed invention in the treatment of any

disease by in vivo or ex vivo gene therapy. No specific examples are provided for a given disease and its requisite pharmaceutical composition, dosage, or methodology for in vivo administration that would constitute an enabling disclosure for a pharmaceutical composition. The claimed invention is said to be "based on the demonstration that different cell types, other than those naturally producing antibodies are capable, after genetic modification, of producing antibodies in a stable fashion *in vivo*" (p. 4, lines 4-6). This is not a novel finding (for example, see Wright et al., Curr. Rev. Immunol., 12(3,4):125-168, 1992 and 35 U.S.C. 102 rejections below). Moreover, although the claims recite "elements guaranteeing the expression in vivo of said antibody gene and the secretion in the blood circulation of a mammal..." (e.g. cl. 16) the specification does not teach what these elements are or how to make embodiments comprising such elements that are commensurate in scope with the claimed invention. For example, the specification states that "[i]n addition to the antibody gene and its promoter, the nucleic acid sequence can include a termination sequence of the transcription, situated downstream from the antibody gene and permitting the secretion of antibody gene product in the blood circulation of the mammal..." (p. 5, lines 14-17). The specification does not give any examples of what these "termination sequence[s]" are or how they "guarantee" or "permit" secretion in the blood circulation of the mammal. Although there is reference to intracellular expression of DNA sequences coding for antibodies (by others) which are "characterized by the fact that they include an antibody gene modified so that the antibody is not secreted (p. 3, last paragraph), and despite the assertion that the claimed invention, "aims, on the other hand, to implement the *in vivo* expression of antibody

genes by cells which secrete said antibodies in the blood circulation of the mammal" (p. 4, 1st paragraph), the instant disclosure does not teach appropriate elements guaranteeing or permitting in vivo expression of the therapeutic antibodies in the blood circulation, such as signal peptide sequences to facilitate secretion.

Considering the lack of predictability and nature of the art, the limited in vivo experiments disclosed (pp. 15-16) carry no predictive value of therapeutic efficacy in considering the enablement of the claimed invention. There is no evidence on record to suggest that implantation in syngenic mice of genetically modified cells producing 100 ng/ml of some unspecified antibody (as recited on p. 15, lines 16-22) has any therapeutic value, nor the suggestion of absence of immune response following implantation of primary myogenic cells expressing a mouse-derived monoclonal antibody (Tg10) in mice. There is no evidence on record to suggest that expression of Tg10 antibodies in mice constitutes any sort of appropriate animal disease model for human disease nor is there any evidence to suggest that secretion of between 100 and 300 ng/ml of Tg10 in the serum for 4 months has any therapeutic value for treatment of a human disease. Immunogenicity of antibodies derived from other species is a recognized problem to the skilled artisan, yet there is no disclosure of therapeutic "humanized" antibodies for use in the pharmaceutical compositions of the claimed invention. Moreover, implantation of genetically-modified antibody-secreting myotubes in mice does not constitute an enabling disclosure that is extrapolatable to humans.

Amount of experimentation necessary. Given the unpredictable and undeveloped state of the art as described above, it would likely require considerable experimentation to appropriately develop the claimed method for treating any disease by gene therapy.

For the reasons discussed above, it would require undue experimentation for one skilled in the art to use the claimed methods. This is particularly true given the state of the art, the nature of the invention, the unpredictability of the art, the scarcity of guidance and working examples in the specification, and the amount of experimentation necessary.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Note: the claims are broadly drawn to 'biological material" comprising a nucleic sequence containing a therapeutic antibody gene or cells comprising said nucleic acid therein. The additional "for use" limitations as applied to "pharmaceutical compositions" and "cells" carry no patentable weight.

Claims 1-4, 6-13 and 20 are rejected under 35 U.S.C. 102(b) as being clearly anticipated by Wright et al. (Crit. Rev. Immunol., 12(3,4):125-168, 1992).

Wright et al. reviews and discloses expression vectors encoding potentially therapeutic antibodies and cells comprising them which are capable of secreting recombinant antibodies into the bloodstream of mammals from genetically-modified nonlymphoid cells or of use in manufacturing genetically-modified cells comprising recombinant antibodies in vivo or ex vivo in a mammalian host (see pp. 130-131, section 6., "Nonlymphoid cell expression").

Wright et al. discloses and reviews biological material comprising expression vectors comprising therapeutic antibody genes with elements *capable* of expressing and secreting into the blood circulation of mammals therapeutically effective amounts of antibody from the vector directly (see for example p. 135-136, section C., "Vectors for immunoglobulin expression" and references therein) or from mammalian cells not naturally producing antibodies which can be genetically modified ex vivo by the antibody gene-containing vector implanted in a mammal (see for example p. 130-131, section 6., "Nonlymphoid cell expression"). The method used to make the products further consititutes a process manufacturing genetically-modified cells comprising recombinant antibodies in vivo or ex vivo in a mammalian host (see pp. 130-131, section 6., "Nonlymphoid cell expression"). Wright also discloses methods for generating various antibody derivative genes, including single-chain antibodies (p. 149-151, section B., "Single-chain Fvs"), as well as methods to increase the half-life of recombinant antibody genes through fusions with Fc domains (p. 154).

Claims 1-4, 12, 13, 15, 16, and 20 are rejected under 35 U.S.C. 102(b) as being clearly anticipated by Stevenson et al. (Ann. N.Y. Acad. Sci., 772:212-226, 1995).

Stevenson et al. disclose injection in a mammal of a vector encoding a therapeutic antibody containing elements *capable* of expressing in the blood circulation of a mouse a therapeutically effective amount or for manufacturing genetically-modified cells comprising therapeutic antibodies in an mammal (see p. 215, middle of page).

Claims 1-10, 12, 13, 15, 16, and 20 are rejected under 35 U.S.C. 102(b) as being clearly anticipated by Moritz et al. (Proc. Natl. Acad. Sci. USA, 91:4318-4322, 1994).

Moritz et al. disclose biological material comprising cells not naturally producing antibodies (e.g. cytotoxic T-lymphocytes) wherein the recombinant antibodies comprise elements *capable* of expressing from a viral vector (retroviral) in the blood circulation of mammals a therapeutically effective amount of a therapeutic antibody directed against a tumor antigen for preclinical and clinical cancer studies or for manufacturing genetically-modified cells comprising therapeutic antibodies.

Claims 1-4, 6-12, 14-16, and 20 are rejected under 35 U.S.C. 102(b) as being clearly anticipated by Chen et al. (Proc. Natl. Acad. Sci. USA, 91:5932-5936, 1994).

Chen et al. discloses cells known not to naturally produce antibodies (COS-1 and CD4+ T lymphocytes) which are genetically modified with recombinant antibody gene-containing

expression vectors for ex vivo gene transfer of said cells or in vivo gene transfer of said vectors for secretion of the recombinant antibodies into the blood circulation of mammals (see abstract and p. 5934).

Conclusion

In light of the broad claims recited, the following examples of prior art, while not relied upon, are provided inasmuch as they may anticipate various embodiments covered by the present claims. Along with the U.S.C. 102 rejections above, these are provided for additional consideration in advance of potential claim amendments arising in the prosecution of this application:

1)	US 5,892,019	Filing Date:	9/1/94	Date of Patent:	4/6/99
2)	US 5,853,717	Filing Date:	5/23/95	Date of Patent:	12/29/98

Certain papers related to this application may be submitted to Art Unit 1632 by facsimile transmission. The FAX number is (703) 308-4242 or 305-3014. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If applicant *does* submit a paper by FAX, the original copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Peter Brunovskis whose telephone number is (703) 305-2471. The examiner can normally be reached on Monday through Friday from 8:30 AM to 5 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jasemine Chambers, can be reached at (703) 308-2035.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

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